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Ranolazine in refractory and chronic stable angina

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Aim/Objectives: The current Scottish Intercollegiate Guidelines Network (SIGN) guidelines recommend beta blockers and dihydropiridine calcium channel blockers as first-line agents for refractory angina pectoris. Despite being optimally treated with pharmacotherapy and revascularisation, up to 40% of patients still experience symptoms.

Ranolazine, a piperazine derivative, selectively inhibits late sodium currents and is of particular interest as it is currently not recommended routinely by SIGN guidelines and Scottish Medicine Consortium (SMC) but has been prescribed in Tayside, initially through IPTR since 2017 and recently through a Local New Medicine Treatment Protocol and Stable Angina Pathway. Real world experience of ranolazine prescribing in patients with chronic and often refractory angina is not widely reported. We therefore audited its use in Tayside to understand its prescribing pattern within our patient population and assess its effects on angina symptom relief.

Methods: Electronic health records and prescribing data between 1st January 2012 and 31st December 2018 were retrospectively analysed. Data on baseline characteristics, prescribing information, past medical history, and angina symptom control were collected. Standard descriptive statistics were used for analysis.

Results: 35 patients were identified as suitable for inclusion in the audit. Mean age was 71.4 ± 12.5 years old and 68.6% were male. 23 patients (65.7%) had either a previous percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG). The most common reason for ranolazine prescription was refractory angina (74.3%) with 375 mg BD being the most common dose. Prescription of guideline-recommended anti anginals was high with 80% of patients being on a beta blocker and a nitrate prior to commencing ranolazine. Encouragingly, 27 patients (77.1%) reported an improvement in Canadian Cardiovascular Society (CCS) angina class and the rate of non-responders was 22.9%. No adverse effects leading to discontinuation of ranolazine was found.

Conclusion: Ranolazine may play a role as an additional anti anginal agent with reasonable achievement of symptom control in patients who have refractory angina despite the use of other guideline-recommended anti anginal agents.

Keywords: Heart rate • Ischemia • Ranolazine • Angina • Acute coronary syndrome

Introduction

The 2019 European Society of Cardiology guidelines for CCS recommend the use of ranolazine as an adjunct therapy for those not controlled by first line treatments.1 The guidance highlights the importance of tailoring pharmacological therapies to patient specific characteristics and preferences. It states that ranolazine should be considered as a second line therapy to reduce the number of angina episodes and to improve exercise tolerance in those who cannot tolerate, or their symptoms are not controlled by, beta-blockers, calcium channel blockers or long acting nitrates. Additionally, ranolazine may be considered as a first line therapy in patients with low heart rate and blood pressure [1]. The National Institute for Health and Care Excellence (NICE) Stable Angina Management Guidelines (2011) give similar recommendations. It states that ranolazine may be used as a monotherapy if beta blockers or calcium channel blockers cannot be used or tolerated. The NICE guidance also recommends that ranolazine may be added in addition to beta blocker or calcium channel blocker monotherapy if the patient's symptoms are not controlled and the other first line therapy is contraindicated [2].

The Scottish Intercollegiate Guidelines Network (SIGN) provides alternative recommendations with regards to the use of ranolazine in the management of stable angina. SIGN describes the evidence regarding ranolazine efficacy as conflicting [3-5].

In 2012, the Scottish Medicines Consortium (SMC) did not approve ranolazine to be used as an add on therapy for stable angina in those who cannot tolerate first line therapies or who are symptomatic despite their use. Consequently, special approval had to be requested for its use in Scotland. This was the case in Tayside, Scotland initially through Individual Patient Treatment Request and latterly through a Local New Medicine Treatment Protocol and Stable Angina Pathway. The aim of this study was to establish the current ranolazine prescribing practices in a large Scottish teaching hospital and to assess its impact and tolerability within our patient cohort on angina symptom relief.

Methods

We retrospectively analysed health records of patients who were prescribed Ranolazine for either chronic stable angina or refractory angina in our hospital between 1st January 2012 to 31st December 2018. As Ranolazine is not currently recommended as an anti anginal agent by the Scottish Medicines Consortium (SMC) therefore prescribing was on a case by case basis. The responsible clinician was required to complete an individualised patient treatment request (IPTR) and to review the patient's symptoms in 4 weeks to ensure improvement in symptoms. Patients who were prescribed ranolazine were deemed to not be suitable for percutaneous coronary intervention/coronary artery bypass graft surgery (CABG), or have already had revascularisation but remained symptomatic with no further invasive treatment options. Data on demographics, treatment indication, and previous intervention, concomitant anti anginal agents, Ranolazine dose, and whether there was an improvement in Canadian Cardiovascular Society symptoms were collected. Descriptive statistics were displayed as mean ± standard deviation for continuous variables and numbers and percentages for categorical variables. This study was approved by the local institutional review board for data collection and analysis.

Results

35 patients were identified as suitable for inclusion in the audit. Mean age was 71.4 ± 12.5 years old and 68.6% were male (Table 1).

Table 1: *Baseline characteristics.*

Characteristic	Ranolazine group (n=35)
Age, years (mean ± SD)	71.4 ± 12.5
Age of first prescription, years (mean ± SD)	69.1 ± 12.1
Duration on Ranolazine, years (mean ± SD)	3.0 ± 2.2
Male	68.60%

23 patients (65.7%) had either a previous percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) (Table 2). The most common reason for ranolazine prescription was refractory angina (74.3%) with 375 mg BD being the most common dose (62.9%) (Table 2).

Table 2: *Symptom and treatment characteristics.*

Characteristic	Frequency (%)
Previous PCI	19 (54.3%)
Previous CABG	10 (28.6%)
Previous CABG and PCI	6 (17.1%)
No previous CABG or PCI	12 (34.3%)
Reason for prescription	
Recurrent angina	26 (74.3%)
Chronic stable angina	5 (14.3%)
No intervention options	3 (8.6%)
Part of research trial	1 (2.9%)
Concurrent medications	
Beta blocker	30 (85.7%)
Nitrates	32 (91.4%)
Calcium channel blocker	11 (31.4%)
Nicorandil	13 (37.1%)
Ivabradine	4 (11.4%)
Ranolazine dose prescribed	
375 mg BD	22 (62.9%)
500 mg BD	12 (34.3%)
750 mg BD	1 (2.9%)
Effect on symptoms	
No change	8 (22.9%)
Improvement in CCS class	27 (77.1%)
Class II to Class I	22 (81.5%)
Class III to Class II	5 (18.5%)
Concomitant anti-anginals	
1 agent	3(8.6%)
2 agents	12(34.3%)
3 agents	16(45.7%)
4 agents	4(11.4%)

Prescription of other guideline-recommended anti anginal agents was high with 80% of patients being on a beta blocker and a nitrate prior to commencing ranolazine (Table 3). Encouragingly, 27 patients (77.1%) reported an improvement in Canadian Cardiovascular Society (CCS) angina class and the rate of non-responders was 22.9% all of whom eventually discontinued Ranolazine use. No adverse effects leading to discontinuation of ranolazine was found.

Table 3: *Other antianginal agents.*

Combination	Frequency (%)
Beta blockers and nitrates	28(80%)
Beta blockers and dihydropyridine calcium channel blockers	9(25.7%)
Beta blockers, calcium channel blockers, and nicorandil	3(8.6%)
Beta blockers, calcium channel blockers, and nitrates	9(25.7%)
Beta blockers, calcium channel blockers, ivabradine	1(2.9%)

Discussion

We report real world data on the use of Ranolazine in patients with refractory angina and chronic stable angina not amenable to further revascularisation. Overall, patients in our centre were treated with good combination of guideline directed medical therapy (GDMT) with 45.7% of patients taking 3 other anti-anginal agents prior to the addition of Ranolazine, reflecting judicious prescribing practice. The majority of patients (80%) were on a beta blocker and a nitrate. Despite this, improvement in CCS angina class was still observed in 77.1% of patients, a finding that is similar to previous work by Bennet et al in a 1-year prospective registry of 100 refractory angina patients [6]. Tolerability was good as we did not find any evidence of side effects in the 35 patients studied. The maximum dose required was 500 mg BD in all of our patients except one. This could of course partially explain the lack of observed side effects.

Refractory angina is defined as angina in the setting of coronary disease of more than 3 months' duration, not adequately controlled with optimal medical therapy (OMT), percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) and where reversible myocardial ischaemia has been established as the cause of the symptoms.7 This group of patients often prove challenging to manage and although no precise figures of the scale of the problem is available, it is estimated that there are around 16,500 new cases per year in England alone [7]. This is likely to increase as coronary artery disease (CAD)-related survival improves in an increasingly ageing population.

The most recent European Society of Cardiology (ESC) guidelines on management of chronic coronary syndromes (2019) lists Ranolazine as a potential third agent of choice in managing angina. This is largely guided by the usual limiting factors of heart rate, blood pressure, and the presence of concomitant left ventricular (LV) systolic dysfunction as well as patient's characteristics and preferences. It is unclear whether combination therapy with two agents is superior to monotherapy with any class of drugs in reducing clinical events [8]. Beta blockers and/or calcium channel blockers are recommended first line agents, based on meta-analyses of RCTs without mortality endpoints as it is widely accepted that the main focus of stable angina treatment is symptom management rather than achieving mortality benefit [1,9].

Ranolazine is a selective inhibitor of late inward sodium channel current (INaL). It reduces intracellular calcium overload during ischaemia, oxidative stress, and LV hypertrophy with a resultant effect of improvement in oxygen demand-supply mismatch. Although there have been 4 randomised controlled trials focusing on Ranolazine use instable angina patients as well as patients with acute coronary syndrome (ACS), real world data on patients with refractory and/or chronic stable angina is scarce [10-13]. This could partially explain the discrepancy in prescribing practice among hospitals in the United Kingdom. Our audit over a period of 6 years in a large teaching hospital in Scotland with certain prescribing restrictions in place, has provided further data to support the potential incremental benefit of Ranolazine in addition to other GDMT anti anginal agents in this population of patients as well as its tolerability.

This was a retrospective audit and therefore has several known limitations. The non-randomised nature of the data subjects the findings to unknown residual confounders. It was also a single-centre experience and therefore limits its generalizability to other patient populations. Furthermore, the lack of side effects seen could be related to the majority of patients being on a maximum dose of 500 mg BD as the majority of side effects are more likely to occur at the higher end of the dose spectrum. We also did not set out to investigate the antiarrhythmic properties of Ranolazine in our patient population, a feature that has previously been attributed to the use of Ranolazine [14]. Nevertheless, the lack of side effects seen and a 77% rate of observed improvement in CCS angina class are encouraging.

Conclusion

In a real world population of refractory angina and chronic stable angina patients not amenable to further revascularisation, the addition of Ranolazine to GDMT may improve symptoms and is well tolerated.

Acknowledments

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References

1. Knuuti J, Wijns W, Saraste A, *et al*. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). Eur Heart J. (2019).
2. (NICE), N.I.o.C.E., Stable angina: management (2011) NICE guideline CG126, in Surveillance report 2016 - Stable angina: management (2011) NICE guideline CG126. 2016, National Institute for Health and Care Excellence (UK): London.
3. Guidelines, S.I.N., Management of stable angina SIGN 151. 2018(2018;(April).
4. Salazar CA, Basilio Flores JE, Veramendi Espinoza LE, et al. Ranolazine for stable angina pectoris. Cochrane Database Syst Rev. 2: Cd011747 (2017).
5. Banon D, Filion KB, Budlovsky T, et al. The usefulness of ranolazine for the treatment of refractory chronic stable angina pectoris as determined from a systematic review of randomized controlled trials. Am J Cardiol. 113(6): 1075-1082 (2014).
6. Bennett NM, Iyer V, Arndt TL, et al. Ranolazine refractory angina registry: 1-year results. Critical pathways in cardiology. 13(3): 96-98 (2014).
7. Sainsbury PA, Fisher M, de Silva R. Alternative interventions for refractory angina. Heart. 103(23): 1911-1922 (2017).
8. Klein WW, Jackson G, Tavazzi L. Efficacy of monotherapy compared with combined antianginal drugs in the treatment of chronic stable angina pectoris: a meta-analysis. Coronary artery disease. 13(8): 427-36 (2002).
9. Belsey J, Savelieva I, Mugelli A, et al. Relative efficacy of antianginal drugs used as add-on therapy in patients with stable angina: A systematic review and meta-analysis. European J Prev Cardiol. 22(7): 837-48 (2015).
10. Chaitman BR, Skettino SL, Parker JO. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J Am Coll Cardiol. 43(8): 1375-1382 (2004).
11. Chaitman BR, Pepine CJ, Parker JO, et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. Jama. 291(3): 309-316 (2004).
12. Stone PH, Gratsiansky NA, Blokhin A, et al. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. J Am Coll Cardiol. 48(3): 566-575 (2006).
13. Morrow DA, Scirica BM,Karwatowska-Prokopczuk E, et al. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. Jama. 297(16): 1775-83 (2007).
14. Bazoukis G, Tse G, Letsas KP, et al. Impact of ranolazine on ventricular arrhythmias - A systematic review. Journal of arrhythmia. 34(2): 124-128 (2018).